WO9933794A1: .ohgr.-CYCLOALKYL-PROSTAGLANDIN E2 DERIVATIVES

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Inventor(s): **TANI, Kousuke** , Ono Pharmaceutical Co., Ltd., Minase Research Institute, 1-1, Sakurai 3-chome, Shimamoto, Japan
OHUCHIDA, Shuichi , Ono Pharmaceutical Co., Ltd., Minase Research Institute, 1-1, Sakurai 3-chome, Shimamoto, Japan

Applicant(s): **ONO PHARMACEUTICAL CO., LTD.**, 1-5, Doshomachi 2-chome, Chuo-ku, Osaka-shi, Osaka541-8526, Japan

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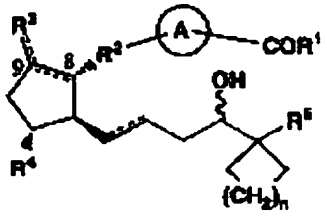
Application Number: **WO1998JP0005863**

IPC Class: C07C 405/00;

Designated Countries: JP, KR, US, **European patent:** AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

Abstract: .ohgr.-Cycloalkyl-prostaglandin E2 derivatives of formula (I) (wherein all symbols are as defined in the description); and non-toxic salts thereof, prodrugs thereof and cyclodextrin clathrates thereof. Compounds of formula (I) strongly bind on the EP2 subtype receptor. Therefore, they are useful for prevention and/or treatment of immunological diseases (autoimmune diseases, organ transplantation, etc.), asthma, abnormal bone formation, neuronal cell death, liver damage, abortion, premature birth or retina neuropathy of glaucoma, etc.
[Show "fr" Abstract]

Representative Image:



(I)

Attorney, Agent, or Firm: **OHIE, Kunihisa;**

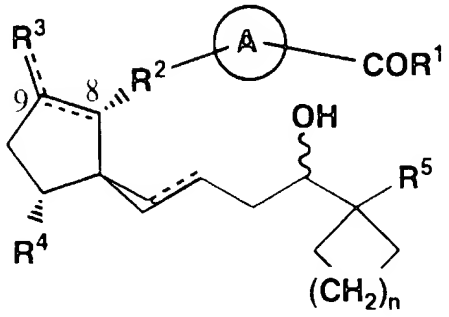
Foreign References: **none**

(No patents reference this one)

DB7

CLAIMS

1. An ω-cycloalkyl-prostaglandin E derivative of formula (I)



(I)

[wherein A is benzene, thiophene or furan ring;

R^1 is hydroxy, C1-6 alkoxy or a group of formula

$$NR^{10}R^{11}$$

(wherein R^{10} and R^{11} are each independently, hydrogen atom or C1-4 alkyl));

R^2 is C1-4 alkylene, C2-4 alkenylene, -S-C1-4 alkylene, -S-C2-4 alkenylene or C1-4 alkylene-S-;

R^3 is oxo, methylene, halogen atom or a group of formula

$$R^{32}-COO-$$

(wherein R^{32} is C1-4 alkyl, C1-4 alkoxy, phenyl, phenyl-C1-4 alkyl, R^{33}-OOC-C1-4 alkyl or R^{33}-OOC-C2-4 alkenyl (wherein R^{33} is hydrogen atom or C1-4 alkyl);

R^4 is hydrogen atom, hydroxy or C1-4 alkoxy;

R^5 is C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, or C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1-3 substituents selected from (1)-(5) below:

(1) halogen atom,

(2) C1-4 alkoxy,

(3) C3-7 cycloalkyl,

(4) phenyl or

(5) phenyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkyl, C1-4 alkoxy, nitro or trifluoromethyl);

n is 0-4;

.....

is single bond or double bond,

with the proviso that when the C8-9 position is double bond, R^3 is a group of

$$R^{32}-COO-$$

(wherein R^{32} is as defined above) and R^2 is C1-6 alkoxy]

or a non-toxic salt thereof or a cyclodextrin clathrate thereof.

2. A compound according to claim 1, wherein A is a benzene ring.

3. A compound according to claim 1 or claim 2, wherein R^1 is C1-4 alkylene or C2-4 alkenylene.

4. A compound according to claim 1 or claim 2, wherein R^2 is -S-C1-4 alkylene, -S-C2-4 alkenylene.

5. A compound according to claim 1 or claim 2, wherein R^2 is C1-4 alkylene-S-.

6. A compound according to claim 3, which is

(1) (11 α, 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,

(2) (11 α, 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13,19-dienoic acid,

(3) (11 α, 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-19,20-methano-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,

(4) (11 α, 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-19-methyl-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,

(5) (11 α, 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-1,6-(p-phenylene)-2,3,4,5,20-pentanorprost-13-enoic acid,

(6) (9 β, 11 α, 13E)-9-Chloro-11,16-dihydroxy-17,17-propano-19,20-methano-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,

(7) (9 β, 11 α, 13E)-9-Chloro-11,16-dihydroxy-17,17-propano-19-methyl-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,

(8) (9 β, 11 α, 13E)-9-Chloro-11,16-dihydroxy-17,17-propano-1,6-(p-phenylene)-2,3,4,5,20-pentanorprost-13-enoic acid or

(9) (9 β, 11 α, 13E)-9-Chloro-11,16-dihydroxy-17,17-propano-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13,19-dienoic acid or a methyl ester thereof.

7. A compound according to claim 4, which is

(1) (11 α, 8Z, 13E)-9-Acetyloxy-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5,20-pentanorprost-8,13-dienoic acid methyl ester,

(2) (11 α, 8Z, 13E)-9-Acetyloxy-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-8,13-dienoic acid methyl ester,

(3) (11 α, 8Z, 13E)-9-Acetyloxy-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-8,13,19-trienoic acid methyl ester,

(4) (11 α, 8Z, 13E)-9-Acetyloxy-11,16-dihydroxy-19-methyl-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-8,13-dienoic acid methyl ester or

(5) (11 α, 8Z, 13E)-9-Acetyloxy-11,16-dihydroxy-17,17-

propano-19,20-methano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-8,13-dienoic acid methyl ester.

8. A compound according to claim 4, which is

(1) (11 α, 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5,20-pentanorprost-13-enoic acid,

(2) (11 α, 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid,

(3) (11 α, 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13,19-dienoic acid,

(4) (11 α, 13E)-9-Oxo-11,16-dihydroxy-19-methyl-17,17-propano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid or

(5) (11 α, 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-19,20-methano-7-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid

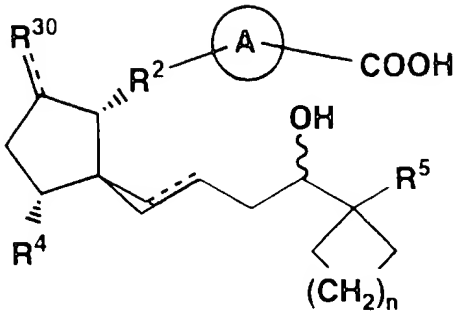
or a methyl ester thereof.

9. A compound according to claim 5, which is

(1) (11 α, 13E)-9-Oxo-11,16-dihydroxy-17,17-propano-6-thia-1,6-(p-phenylene)-2,3,4,5-tetranorprost-13-enoic acid

or a methyl ester thereof.

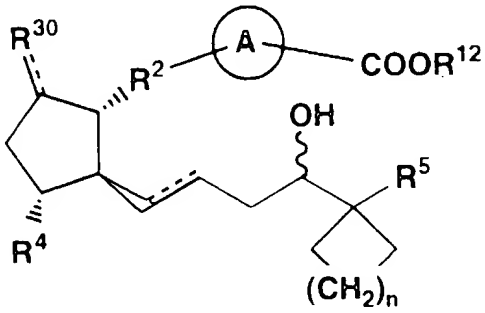
10. A process for the preparation of a compound of formula (IA)



(IA)

(wherein R^{30} is oxo, methylene or halogen atom and the other symbols are as defined in claim 1)

characterized by subjecting a compound of formula (IB)

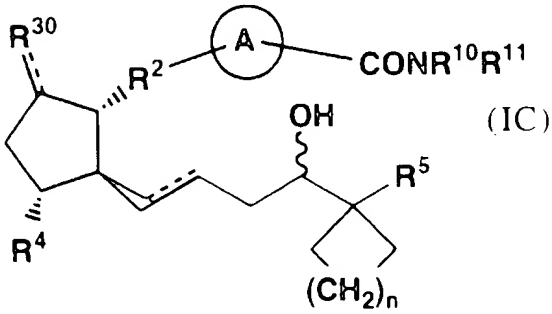


(IB)

(wherein R^{12} is C1-6 alkyl and the other symbols are as defined above)

to hydrolysis using an enzyme or hydrolysis under alkaline conditions.

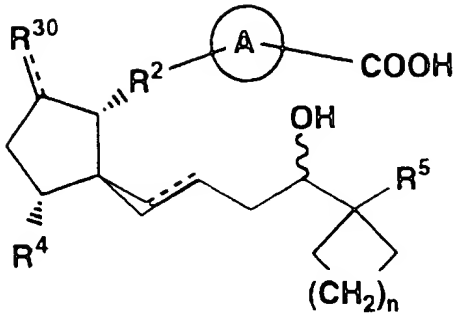
11. A process for the preparation of a compound of formula (IC)



(IC)

(wherein R^{30} is as defined in claim 10, and the other symbols are as defined in claim 1)

characterized by subjecting to amidation a compound of formula (IA)



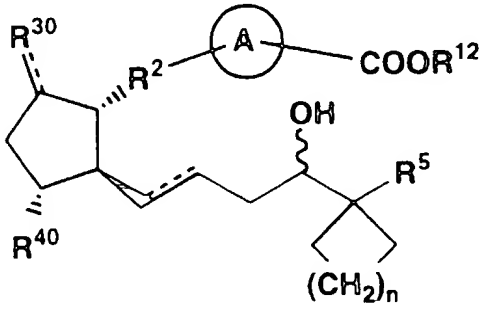
(IA)

(wherein all symbols are as defined above)
and a compound of formula (II)

$$HR^{10}R^{11} \quad (II)$$

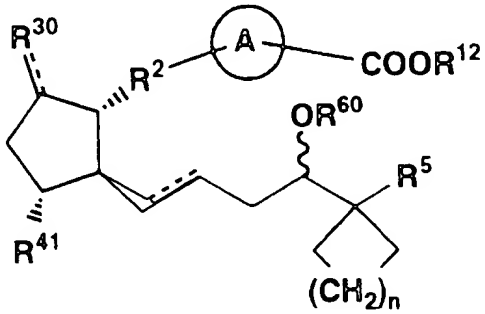
(wherein all symbols are as defined above).

12. A process for the preparation of a compound of formula (IB-1)



(IB-1)

(wherein R^{40} is hydrogen atom or hydroxy, R^{12} and R^{30} are as defined in claim 10, and the other symbols are as defined in claim 1) characterized by subjecting to deprotection under acidic conditions a compound of formula (III)

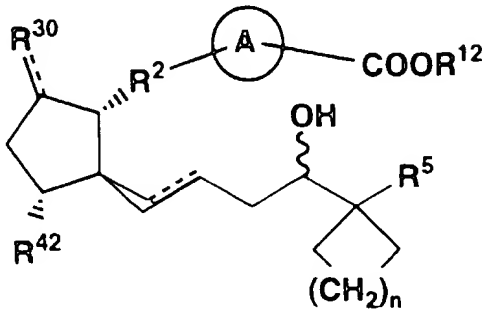


(III)

(wherein R^{41} is hydrogen atom or hydroxy protected by a group which may be removable under acidic conditions, R^{60} is a protective group

for hydroxy which may be removable under acidic conditions, and the other symbols are as defined above).

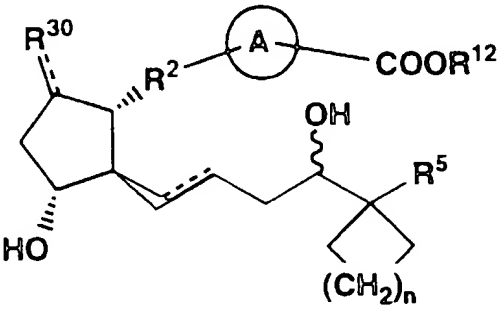
13. A process for the preparation of formula (IB-2)



(IB-2)

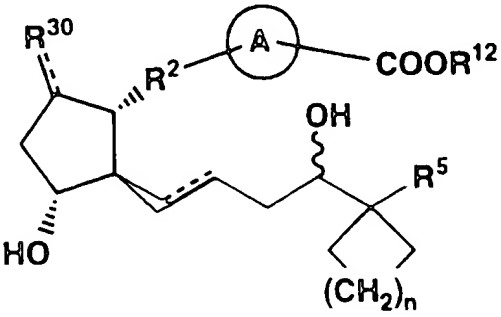
(wherein R^{42} and R^{30} are as defined in claim 10, R^{42} is C1-4 alkoxy, and the other symbols are as defined in claim 1)

characterized by subjecting to O-alkylation a compound of formula (IB-3)



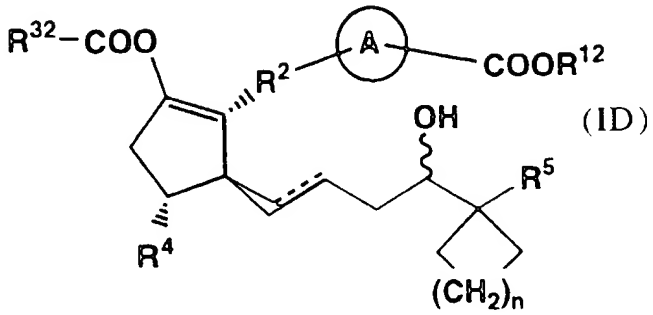
(IB-3)

(wherein all symbols are as defined above).



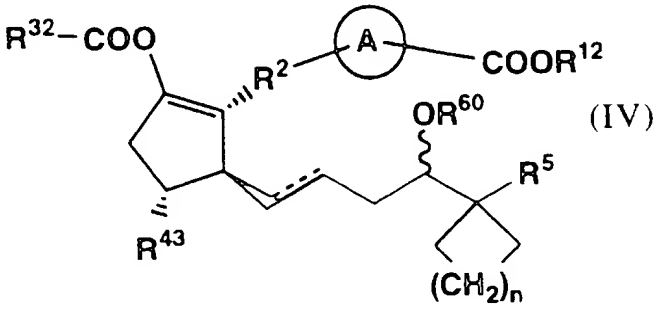
(IB-3)

14. A process for the preparation of a compound of formula (ID)



(ID)

(wherein R^{12} is as defined in claim 10, R^{32} is as defined in claim 1, and the other symbols are as defined in claim 1) characterized by subjecting to deprotection under acidic conditions a compound of formula (IV)



(IV)

(wherein, R^{43} is hydrogen atom, hydroxy protected by a group which may be removable under acidic conditions or C1-4 alkoxy, R^{60} is as defined in claim 12, and the other symbols are as defined above).

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/JP 98/05863

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C405/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 132 738 A (KLUENDER HAROLD C ET AL) 2 January 1979 cited in the application see claims	1-14
Y	V. KOZMIK ET AL.: "SYNTZHETIC ANALOGUES OF PROSTAGLANDINS F2ALPHA AND E2" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS.. vol. 59, 1994, pages 138-148, XP002099715 PRAGUE CS see page 139	1-14

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 April 1999	03/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/JP 98/05863

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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